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The Design of Potential Anti-Parkinsonian Drugs: What is the Dopaminergic Pharmacophore in Ergot Alkaloids?¹

JOSEPH G. CANNON

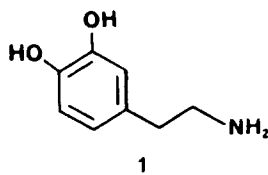
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The problem of defining structural similarities between apomorphine and certain ergot alkaloid derivatives, two chemically dissimilar types of drugs having similar pharmacological effects, is addressed by considering the three-dimensional geometry of the molecules. Conformational analytical concepts can be used to design new chemical entities and to assess structure-activity relationship hypotheses, and indeed this strategy has led to synthesis of new categories of potentially clinically valuable agents.

Some conclusions are presented with respect to the combinations of atoms within the molecules in various chemical categories of dopaminergic agonists, which are responsible for the observed pharmacological effects. On the basis of these conclusions, some general properties of *in vivo* dopamine receptors are inferred, and proposals are advanced for structural analysis of the molecule of dopamine itself, which may be applicable to the design of new, superior therapeutic agents for those pathological conditions which are referable to the dopaminergic nervous system.

INDEX DESCRIPTORS: dopaminergic pharmacophore; ergot alkaloids; structure-activity relationships; drug design

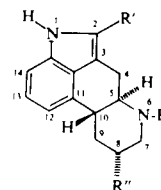
The biochemical involvement of the neurotransmitter substance dopamine 1 in the Parkinsonian syndrome is well established, and the most successful therapeutic strategy has been the administration of a drug (either a biochemical precursor to dopamine itself, or a synthetic dopaminergic agonist), for the purpose of stimulating the remaining, intact hyperresponsive dopamine receptors in the nigrostriatal pathway in the brain, in order to relieve the abnormalities of muscular control.



Among the agents which have elicited some clinical interest is a semi-synthetic derivative of the ergot alkaloid family, a derivative of the ergoline ring system, *bromocriptine* 2. Indeed, dopaminergic agonist effects have been noted in a variety of ergoline derivatives: lergotril 3, pergolide 4, and lisuride 5, in addition to bromocriptine. It is established that the significant biological effects of these compounds reside in the ergoline ring system, and not in the variety of complex substituents on the molecule. In addition to their effects on dopaminergic mechanisms, many of the ergolines have a high affinity for α -adrenoceptors and for serotonin receptors.

Thus, the pharmacologic profile noted for these drugs is the sum total of their effects on dopamine receptors, norepinephrine α -receptors, and serotonin receptors. It seems probable that any drug derived from the ergoline ring system will possess a broad spectrum of side effects. Certainly, one of the most important features of any clinically useful anti-Parkinsonian agent must be a high degree of pharmacologic specificity and freedom from serious side effects. An added complication is the fact that lergotril 3 is metabolized to a 13-hydroxy metabolite 6 which is exponentially more potent than lergotril itself in several animal assays (2), and which is believed to be responsible for the preponderance of the observed dopaminergic effects of the drug. It

¹This work was presented at the College of Pharmacy Centennial Symposium, The University of Iowa, Iowa City, September 12-13, 1985.



3. Lergotril

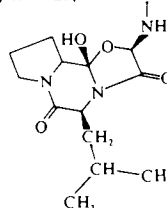
R = CH₃; R' = Cl; R'' = -CH₂CN

4. Pergolide

R = n-C₃H₇; R' = H; R'' = -CH₂-S-CH₃

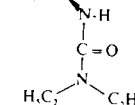
2. Bromocriptine

R = CH₃; R' = Br; R'' = -C(=O)NH₂; $\Delta^{9,10}$

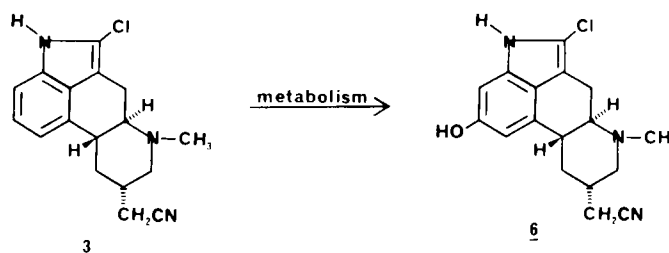


5. Lisuride

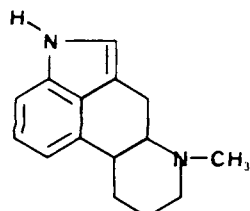
$\Delta^{9,10}$; R = CH₃; R' = H



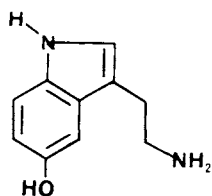
is appealing to propose that lergotril is a prodrug to its 13-hydroxy metabolite. However, not all of the ergot derivatives require this metabolic activation; bromocriptine, for example, is active as such.



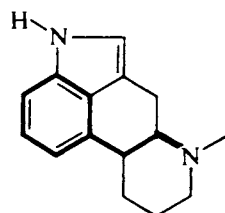
The observed effects of these molecules at *serotonin* receptors can be rationalized. It is apparent that the ergoline system **7** contains an indole-3-ethylamine moiety analogous to serotonin **8**; thus, the ergolines may have an affinity for serotonin receptors because the receptors recognize the ergoline ring as being structurally like serotonin.



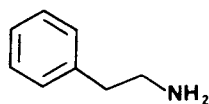
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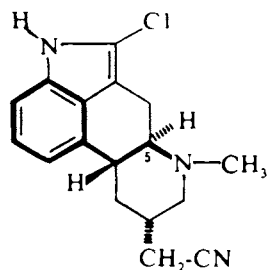
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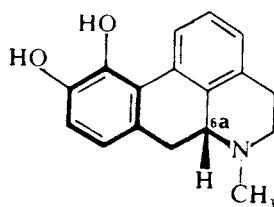
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However, rationalization of a close structural similarity between the ergoline derivatives and dopamine is not quite as obvious or facile. While there is a β -phenethylamine moiety **10** in the ergoline system analogous to that in dopamine (illustrated in structure **9**), the ergoline system in several very potent dopaminergic molecules lacks the catechol di-OH moiety of dopamine (and, indeed, sometimes lacks any phenolic groups whatsoever). It is well established that unsubstituted β -phenethylamine **10** is devoid of effects at dopamine receptors, and it is this combination of atoms that is contained in most of the dopaminergic ergoline derivatives. Therefore, the medicinal chemists posed the questions: "What is the dopaminergic pharmacophore in the ergoline ring system?" To what combination of atoms is the affinity of these ergot derivatives for dopamine receptors due?"

Nichols (3) attacked the problem by first noting that the dopaminergically active ergoline derivatives (typified by lergotrile, structure **11**) appear to have the "wrong" absolute configuration at the chiral center (position 5) which forms a part of the β -phenethylamine moiety, in comparison with the analogous carbon (6a) in the biologically active enantiomer, (R)-(-)-apomorphine (structure **12**), a prototyp-

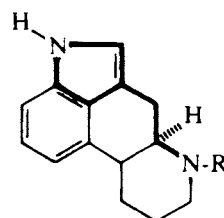


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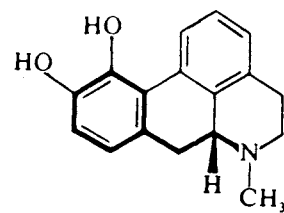


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ical dopaminergic agonist, which is frequently used as a reference standard drug, for comparison with other dopamine-like synthetic agents.

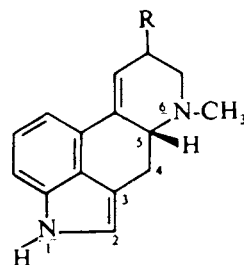


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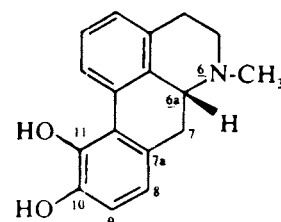


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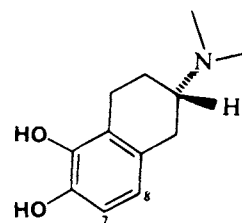
It is apparent that the hydrogen in the ergoline system is pointed back behind the plane of the page, and the equivalent hydrogen in apomorphine is projected out in front of the plane of the page. Nichols rationalized the pharmacological differences in these absolute configurations upon the premise that the rigidly held *pyrrole-3-ethylamine* moiety of the ergoline ring system (outlined in heavy lines in structure **13**) corresponds to the β -3,4-dihydroxyphenethylamine moiety within the apomorphine molecule (outlined in heavy lines in structure **14**), and indeed that this pyrrole ethylamine moiety represents the dopaminergic pharmacophore in the ergolines. The emphasized portion of the ergoline ring system **13** is biochemically equivalent to the emphasized portion of the apomorphine system **14**. Nichols drew the two ring systems from a different perspective to emphasize these ideas.



15



16

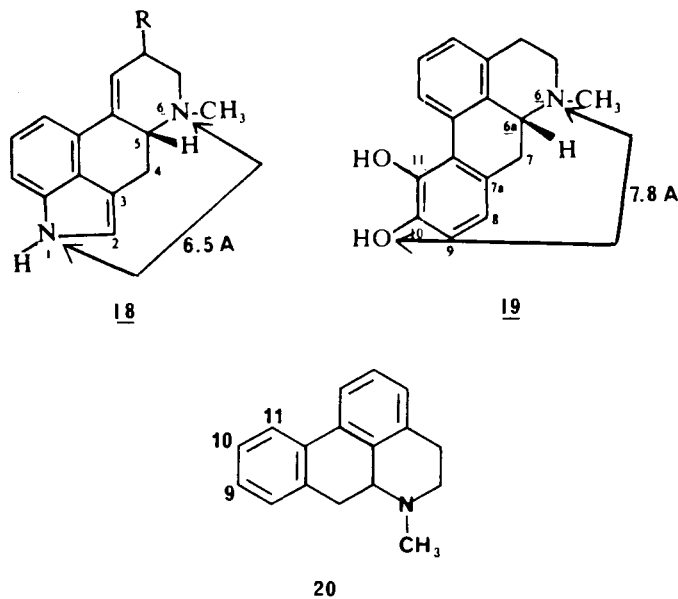


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In **15**, the ergoline ring system has been turned on its opposite face, and it and the apomorphine molecule **16** have been rotated in the plane of the page. Priority was placed on correspondence at the chiral carbons and the aliphatic ring nitrogen, as shown. The 2,3,4,5,6 positions of the ergoline system were proposed to correspond to and to superimpose upon the 6, 6a, 7, 7a, 8 positions of apomorphine. Thus, the 2- position of the ergolines corresponds to the 8- position of apomorphine and to the 8- position of the 2-aminotetralins **17**. These 2-aminotetralins represent a fragment of the apomorphine molecule, as well as being congeners of dopamine. They have the same

stereochemical properties as apomorphine; they have the same molecular shape and, like apomorphine, they are very potent dopaminergic agonists.

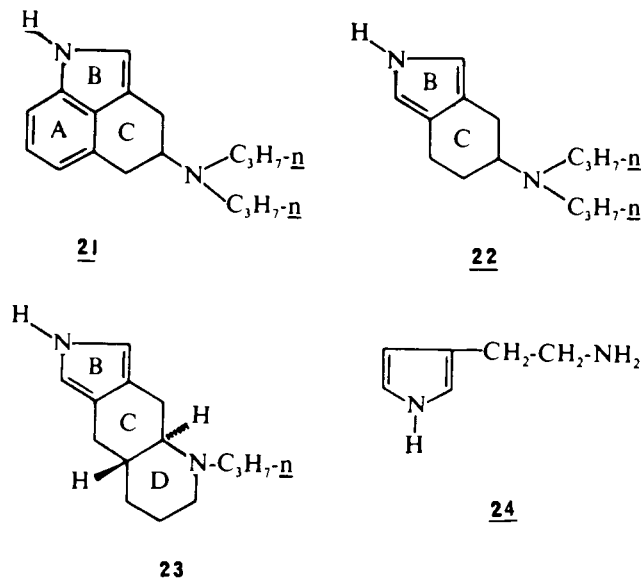
Nichols suggested that the C-10 hydroxy of apomorphine is in about the same position in space relative to the basic nitrogen as is the indole N-H of the ergolines, relative to its basic nitrogen. Analysis of molecular models by us did not confirm this: the distance between N-6 and the indole ring nitrogen (N-1) in the ergoline ring system (structure 18) is approximately 6.5 Å, and the nitrogen-to-C-10 OH distance in apomorphine (structure 19) is approximately 7.8 Å. It seems to follow from the Nichols proposals that the pyrrole ring N-H of the ergolines and the C-10 ("para") OH of apomorphine are biologically equivalent for interaction with the same subsite on the dopamine receptor(s).



However, consideration of pharmacological data (4) on the mono-hydroxylated congeners of apomorphine (structure 20) indicates that the 10-monohydroxy molecule is *not* a direct acting dopaminergic agonist, and is not very active/potent. The 9-hydroxy isomer is inert. Significant dopaminergic effect is present only in the 11-monohydroxy derivative, which does not appear to provide a close superimposition upon the proposed corresponding region in the ergoline system. The Nichols structural correlations are intriguing with respect to comparison of chiral centers, but it seems that the structural ideas involving interatomic distances are less impressive, in that the ergoline structures fit and compare best with structures of *inactive* apomorphine derivatives.

A test of any structure-activity proposal is its utility in design of new agents having the desired biological activity and high potency. Kornfeld and co-workers at Eli Lilly and Company accepted the hypothesis that in the ergoline class, the rigid pyrrole-3-ethylamine moiety rather than the β -phenethylamine moiety is responsible for dopamine agonist properties. To test the hypothesis, they designed and synthesized a series of ergoline partial structures (5).

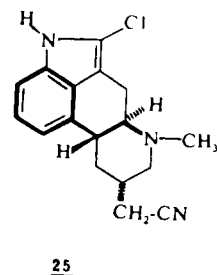
Compound 21 is dopaminergically active, but this structure is a poor choice for the purpose of the study, in that it still contains both the

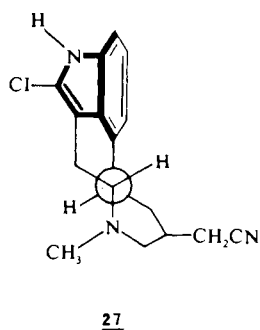
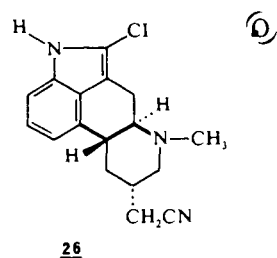


pyrrole-3-ethylamine and the β -phenethylamine moieties. Structures 22 and 23 showed dopamine-like effects, albeit of much lower potency than (*e.g.*) pergolide. These were the first non-benzene derived molecules for which significant dopaminergic effect has been reported. These results were taken as strong support for the hypothesis that the dopaminergic pharmacophore in the ergolines is the pyrrole-3-ethylamine. These molecules bear *n*-propyl groups on the basic nitrogen. It is an empirical observation, noted first by us and subsequently verified many times, that *n*-propyl groups enhance dopaminergic agonist effect, even to the extent of conferring agonist effects upon some molecules that were inert or nearly so when they bore hydrogen or methyl on the basic nitrogen.

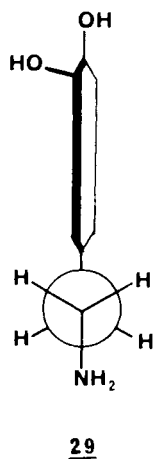
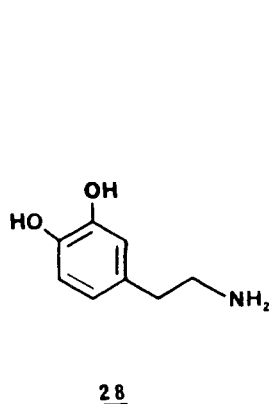
A detriment to the entire argument is the finding by the Eli Lilly group (5) that pyrrole-3-ethylamine 24 is inert *in vivo* as a dopaminergic agonist. Without experimental evidence, this inactivity was rationalized on the basis that this primary amino compound (like exogenous dopamine) is rapidly destroyed *in vivo* by monoamine oxidases. The Lilly group did not report preparation or test data for a *tertiary* amine homolog of this pyrrole-3-ethylamine, which would be refractory to monoamine oxidases and which should, on the basis of their hypothesis, be an active dopaminergic agent.

In contrast to the Nichols-Lilly ideas, our group at the University of Iowa argued that the pharmacophore of ergoline systems is the β -phenethylamine moiety, illustrated (structure 25) with lergotril.





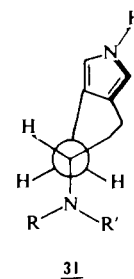
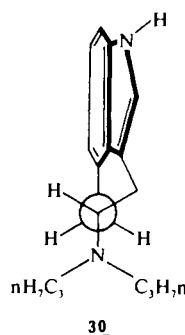
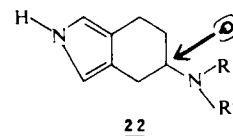
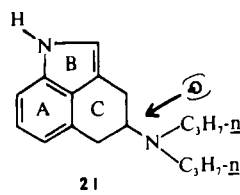
Inspection of molecular models reveals that lergotril is a rigid system and overall, the ring system is planar. Referring to structure 26, if a sight be taken down the ethylamine side chain of the β -phenethylamine moiety within the molecule, with the nitrogen atom (N-6) nearest to the eye, the molecule appears as in the Newman projection 27. The entire indole system of the molecule (heavy lines, structure 27) is planar and, as drawn, the benzene ring and the pyrrole ring project out toward the viewer. The indole ring system is *anti* to the amino nitrogen and, according to our analysis of models, the plane of the benzene-pyrrole rings is approximately 20° out of coplanarity with the ethylamine side chain. This is an excellent overall approximation of what we believe to be one of the biologically significant conformers of the flexible dopamine molecule when it interacts with certain of its receptors: the so-called α -conformation, shown in structure 28 and the Newman projection 29. This is very close to the conformation of the dopamine moiety within the apomorphine molecule.



A significant fact is that the ring nitrogen of indole or pyrrole is not basic, but is weakly acidic. Thus, chemically, the N-H in 27 is not unlike a phenolic OH, and we have proposed that in these systems, this indole ring N-H is bioisosteric with phenol. It occupies the same position in space as does the "meta"-OH of dopamine in the biologically significant α -conformer shown in structure 29. Moreover, our past work, as well as that of others, has consistently indicated that the "meta"-OH of dopamine is unusually important in the interaction of the molecule with its receptors. Interatomic distance measurements indicate that the amino-to-meta OH distance in the dopamine α -conformer is 6.4 Å, and in the lergotril molecule, the distance between the amino N-6 and the indole ring N-H is almost exactly the same. Thus, the presence of a biologically potent conformer of the dopamine molecule can be visualized within the ergoline structure.

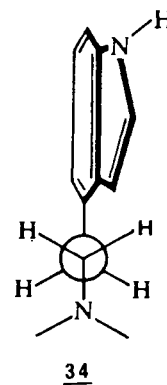
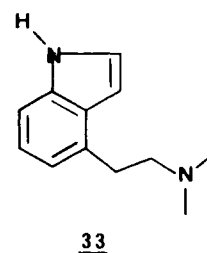
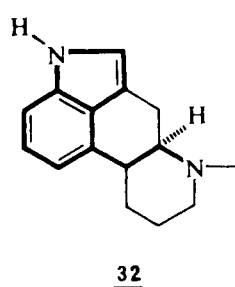
Reasonable conformations of the ergoline ring fragments 21 and 22

(with the diagram showing the eye viewing the appropriate aspect of the molecule) present the basic amino nitrogen and the indole or pyrrole ring nitrogen in the same spatial disposition as the amino nitrogen and the "meta"-OH in the α -conformation of dopamine, illustrated with Newman projections 30 and 31.



In addition, the internitrogen distance in 30 and 31 is approximately 6.2 Å, virtually identical with the N-to-meta OH distance of 6.4 Å in dopamine. It can be speculated that dopamine receptors cannot discriminate between a properly situated indole (or pyrrole) N-H and a phenolic OH, which is a classic example of bioisosterism.

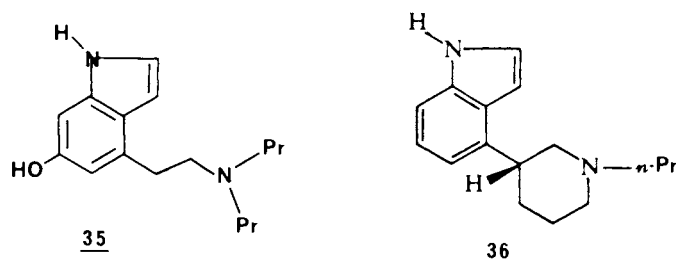
Discussion is pointless, however, unless these ideas can be used to design new, potent/active molecules. Our premise, based upon our conformational ideas, was that the dopaminergic pharmacophore in ergolines is the heavily shaded portion in structure 32, an indole-4-ethylamine moiety 33.



Conformational analysis of this indole-4-ethylamine molecule shows that the flexible molecule can assume (*inter alia*) a conformation very similar to that of the analogous sequence of atoms in ergoline systems such as lergotrile, with the indole ring system coplanar with the ethylamine side chain, and projecting out toward the viewer, and with the basic nitrogen and the indole ring system *anti*, as illustrated in 34. This simple molecule is very similar to dopamine itself: it is flexible like dopamine, and it is capable of existing in a dopamine-like α -conformation.

We synthesized compound 33, bearing *n*-propyl groups on the amino group (6). This is an extremely potent/active dopaminergic agonist. Moreover, its pharmacologic effects at dopamine receptors qualitatively and quantitatively parallel those of lergotrile and of certain other ergolines. However, compound 33 lacks effect at serotonin receptors, and it has only weak actions at adrenergic sites. Thus, we have simplified the pharmacology of the ergot-derived dopaminergics, and have created a more specific agent with decidedly fewer side effects.

We noted that, like lergotrile, compound 33 exhibits a 25-30 minute lag period between intravenous administration and production of maximal pharmacologic effect (7). Also, the compound, while very potent *in vivo*, showed only extremely weak effects *in vitro*. In the case of lergotrile 3, the lag time observed for onset of effect was concluded to be due to metabolic conversion to a 13-hydroxy metabolite 6. We speculated that we might be observing similar metabolic activation of our indole system, and we designed a molecule 35 bearing an OH on the ring position analogous to the 13-position of lergotrile (8).



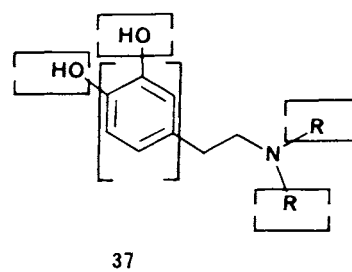
Compound 35 had a very potent/active dopaminergic agonist profile, and the lag time between intravenous administration and maximal pharmacologic response was brief. The compound, unlike the non-oxygenated system 33, was as active *in vitro* as it was *in vivo* (7).

Almost coincident with the communication of our findings on these compounds, Boissier and Nedelec at Roussel-Uclaf (France) (9) described high dopaminergic potency for a similar system 36. Here, the ethylamine side chain of our compound is a part of a piperidine ring system. This Roussel compound also appeared to be metabolically activated *in vivo*. The Roussel workers concluded that the indole-4-ethylamine moiety of ergolines is the dopaminergic pharmacophore. Interestingly, the absolute configuration of the chiral center in the pharmacologically active enantiomer of 36 (as shown) is the same as in the analogous position of the biologically active, naturally-derived ergolines (9). However, an equivalent chiral center does not exist in apomorphine, so that it is not possible to draw structure-activity conclusions. It is regrettable that our simple indole-4-ethylamines have no asymmetric center for possible assessment of the Nichols ideas about stereochemical differences/similarities. Certainly, a weakness of our work (and, to a lesser extent, of the Roussel work) is the inability of our designed compounds to answer or to address the apparent "wrong" stereochemistry between the ergolines and apomorphine.

And, it must be noted that the Eli Lilly group's argument for the pyrrole-3-ethylamine moiety's being the pharmacophoric group of the ergolines was weakened by the almost complete inactivity of the simple pyrrole-3-ethylamine 24. Both the Lilly-Purdue studies and the Roussel-Iowa studies represent reasonable, rational approaches to the problem. Both hypotheses about the nature of the dopaminergic pharmacophore in ergots seem logical, and both have led to the design of dopaminergic agonists having potential clinical utility. However, neither hypothesis was adequate to explain pharmacological results on all of the compounds studied, and neither hypothesis permitted an unequivocal, universally acceptable definition of the dopaminergic pharmacophore. Neither hypothesis by itself nor the pharmacologic data collected by the proponents of either hypothesis was sufficient to permit the construction of a graphic representation of the topography of any dopamine receptor.

The most that we can all agree upon is that significant components of the ergoline ring system for dopaminergic agonism seem to be the basic nitrogen (capable of bearing a unit positive charge) and the indole ring N-H which presumably (like a phenolic OH) can act as a facile proton donor for hydrogen bonding with a receptor. Moreover, a molecule incorporating these two groups in an appropriate steric relationship to each other, with an appropriate inter-nitrogen distance (approximately 6.4 Å) may demonstrate dopamine-like effects.

I believe that the results of our twenty years of active study of dopamine permit us to make some conclusions: Probably many, if not most, of the dopaminergic agonist structure-pharmacology correlations that have been made in the past (by us and by others) are naive and do not necessarily reflect the true nature of dopaminergic agonist-receptor interactions, even though we can frequently use these correlations rationally to design biologically active compounds. It seems increasingly likely that the dopamine receptor protein molecules possess a high degree of flexibility; the protein chain can exist in more than one conformation; these conformations are in equilibrium with each other and are easily interconvertible. The receptors can alter their molecular shapes and the details of their geometry so as to compliment and interact with several functional groups in a drug molecule. And, depending upon the exact nature of the functionalities in the agonist molecule, the receptor can recognize and interact with varying absolute configurations of chiral centers. Moreover, a multiplicity of these different agonist-receptor complexes is capable of eliciting a physiological dopaminergic response. Different chemical series of dopaminergic agonists may be interacting with the same geographic area on the receptor protein molecule but, depending upon the chemical nature of the specific chemical series of agonists, a different conformation of the receptor protein may be involved. Thus, within a *given chemical series* of agonists, there may be a well defined structure-activity and stereochemical correlation. But, these correlations may disappear when a different chemical series of agonists is addressed, and a new combination of structural parameters and stereochemical requirements may apply. If this be true, structural comparisons and correlations between ergoline derivatives, apomorphine derivatives, and other dopaminergic agonist molecular systems may not only be meaningless, but actually may be misleading.



As shown in structure 37, we view the dopamine molecule as comprising three pharmacologically significant structural entities: a system of phenolic OH group(s); a ring system; and substituent(s) on the basic nitrogen, in addition to the absolute three-dimensional geometry of the molecule . . . the stereochemistry of an asymmetric center. Modification of one or more of these four parameters, independent of the others, can result in retention, reinforcement, or destruction of dopaminergic agonist activity of the molecule. We believe that if one parameter (*e.g.*, the phenolic OH groups) is modified so as to destroy dopaminergic activity, then one or more of the other parameters (*e.g.*, the nitrogen substituents or the absolute configuration of an asymmetric center) may be modified at the same time, such that the dopaminergic agonist effect will be *retained* in the molecule. This view derives from the concept that the dopamine receptors are conformationally highly flexible and can accommodate a variety of chemical and stereochemical variations of the dopamine molecule.

If these simple ideas are valid, future structure-activity studies of dopaminergic agonists will be infinitely more difficult and challenging. However, the rewards are vastly improved therapeutic agents, not only against the Parkinsonian syndrome, but for treatment of some types of schizophrenia, essential hypertension, some kinds of cardiac arrhythmias, and perhaps other challenging ailments, will

make the effort eminently worth doing.

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